REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-3, 6-11, 14, 15 and 16 are in the case.

I. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claim 15 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons detailed on page 3 of the Action. In response, and without conceding to the rejection, claim 15 has been amended to clarify the method as being one in which the compound is administered first at 100mg/day or less and then escalated to a maximum treatment dose of 500mg/day to 700mg/day over a period of 1 to 10 weeks. Support for this amendment appears in the present application US2004/0229873A1, paragraph [0021], and is further exemplified in paragraph [0023]. Other claim amendments have been made to improve the form of the claims. No new matter is entered. Withdrawal of the outstanding 35 U.S.C. §112, second paragraph, rejection is respectfully requested.

II. THE OBVIOUSNESS REJECTIONS

Claims 1-3, 6-9 and 11 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bountra *et al*. (Bountra). Claims 10, 14 and 15 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bountra. Claims 1-3, 6-9, 11 and 15 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Lunardi *et al*. (Lunardi). Those rejections are respectfully traversed.

The invention as claimed in claim 1 is directed to a method of treating a patient in need of therapy for multiple sclerosis. The method comprises administering to that patient a therapeutically effective dose between 500mg/day and 700mg/day of a compound of formula I wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, trihaloalkyl and halo substituents; X^1, X^2 and X^3 are independently selected from CH, CCH_2F, CCF_3, CO alkyl and CCH_3, and nitrogen atoms, with at least two of X^1, X^2 and X^3 being nitrogen; and Y^1 and Y^2 are independently selected from hydrogen, NH_2 and tertiary amino groups wherein the tertiary amino groups are selected from -1-piperazinyl and 4-alkyl-1-piperazinyl.

The Action points to Bountra, page 10, lines 1-8. However, this passage is merely a boiler plate disclosure that, for different sodium channel blockers, the physician should take into account the age and condition of the patient. However, this is what the physicians have done in the case of Lunardi in treating multiple sclerosis patients 16-20 with far lower doses of lamotrigine (i.e., 125 mg/day) than other patients (max 400mg/day). Bountra therefore provides more support for encouraging the physician to take account of the patient's condition (multiple sclerosis) and to use a **lower** dose accordingly.

The Action cites to claim 7 of Bountra as a disclosure that sodium channel blockers may be used to treat multiple sclerosis. Applicants have previously provided reference to the fact that carbamazepine, a sodium channel blocker, makes multiple sclerosis worse (Ramsaransing, *et al*). In this regard, Lunardi states that all their patients had been on carbamazepine at 200 to 1500 mg/day prior to lamotrigine treatment, but that this treatment had been stopped due to serious side effects. The

Bountra claim is clearly speculation made without reference to the real human derived data provided by Ramsarangsing and Lunardi. The person of ordinary skill in the art would not therefore have read Bountra as being cognisant of the condition of the patient and then go against the condition to apply still higher doses of a class (sodium channel antagonists) known to be detrimental to multiple sclerosis patients.

Applicants on the other hand teach that the dose be escalated to avoid adverse effects [paragraph 0023]. These effects include common occurrence of skin rash - Guberman *et al.*, Epilepsia (1999) 40(7): 985-991, page 990 Table 3 where a maintenance dose of 200-400mg is used, and Wong *et al*. (1999) Ann. Pharmacotherapy 33:1037-1042 (copies attached). These papers are directed at use of lamotrigine in regard to epilepsy, where a relatively high dose is employed as compared with other conditions. Guberman *et al.* and Wong *et al*. illustrate why a physician, in light of Bountra's disclosure to take note of their patient's condition, would in fact not have been motivated, as of the date of the present application, to use increased doses of lamotrigine.

With regard to a physician's motivation in using lamotrigine in multiple sclerosis patients, pain syndromes common in that disease are a clear target that is addressed by this drug. However, the prior art discloses the lower end of Bountra's scale to be appropriate. Thus, the following post-Bountra papers (copies attached) evidence the exercise of physician's judgement in use of lamotrigine in multiple sclerosis:

Leandri *et al*. (2000) J. Neurol 247:556-558 teaches doses of 25mg up to a maximum of 400mg/day;

Solaro *et al*. (2005) Neurol Sci 25: 307-310 uses 75mg/day to 400mg/day;

Silver *et al*. (2007) Journal of Pain and Symptom Management 34(4): 446-454 uses 200mg/day, 300mg/day and 400mg/day.Breur et al (2007) Clinical Therapeutics 29(9):2022-2030 teaches use of 400mg/day;

Titlie *et al*. (2008) Bratisl Lek Listy 109(9): 421-424 teaches doses of 200mg/day-250mg/day (in post stroke pain).

It will be seen from the state of the art as of the filing date of the present application, as evidenced above, that physicians, post-Bountra, clearly would have interpreted suitable doses as 400mg/day or less. Lunardi likewise does not suggest treatment of multiple sclerosis using the claimed dosage level. Thus, taking Bountra alone, or in combination with Lunardi, the physician would not have been motivated to arrive at the presently claimed dosage of between 500mg/day and 700mg/day and, in fact, would have acted to reduce the dosage in the case of multiple sclerosis patients based on the state of the art. Reconsideration and withdrawal of the outstanding obviousness rejections are accordingly respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

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Solaro *et al*. (2005) Neurol Sci 25: 307-310; Silver *et al*. (2007) Journal of Pain and Symptom Management 34(4): 446-454; Breur et al (2007) Clinical Therapeutics 29(9):2022-2030; Titlie *et al*. (2008) Bratisl Lek Listy 109(9): 421-424